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Meat and meat-mutagen intake and risk of non-Hodgkin lymphoma: results from a NCI-SEER case–control study

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Non-Hodgkin Lymphoma (NHL) incidence has risen dramatically over past decades, but the reasons for most of this increase are not known. Meat cooked well-done using high-temperature cooking techniques produces heterocyclic amines (HCAs) and polycyclic aromatic hydrocarbons (PAHs) such as benzo[a]pyrene (B[a]P). This study was conducted as a population-based case–control study in Iowa, Detroit, Seattle and Los Angeles and was designed to determine whether meat, meat-cooking methods, HCAs or PAHs from meat were associated with NHL risk. This study consisted of 458 NHL cases, diagnosed between 1998 and 2000, and 383 controls. Participants completed a 117-item food frequency questionnaire (FFQ), with graphical aids to assess the meat-cooking method and doneness level, which was linked to a HCA and B[a]P database. Logistic regression, comparing the fourth to the first quartile, found no association between red meat or processed meat intake and risk for NHL [odds ratio (OR) and 95% confidence interval (CI): 1.10 (0.67–1.81) and 1.18 (0.74–1.89), respectively]. A marginally significant elevated risk for NHL was associated with broiled meat [OR and 95% CI: 1.32 (0.99–1.77); *P* trend = 0.09], comparing those who consumed broiled meat with those who did not. The degree to which meat was cooked was not associated with the risk for NHL, although one of the HCAs, DiMeIQx (2-amino-3,4,8-trimethylimidazo[4,5-f]quinoxaline), was associated with an inverse risk. Fat intake was associated with a significantly elevated risk for NHL [OR and 95% CI: 1.60 (1.05–2.45); *P* trend = 0.12]; in contrast, animal protein was inversely associated with risk for NHL [OR and 95% CI: 0.39 (0.22–0.70); *P* trend = 0.004]. Overall, our study suggests that consumption of meat, whether or not it is well-done, does not increase the risk of NHL. Furthermore, neither HCAs nor B[a]P from meat increase the risk of NHL.

Abbreviations: B[a]P, benzo[a]pyrene; CI, confidence interval; DiMeIQx, 2-amino-3,4,8-trimethylimidazo[4,5-f]quinoxaline; FFQ, food frequency questionnaire; HCAs, heterocyclic amines; OR, odds ratio; MeIQx, 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline; NHL, non-Hodgkin lymphoma; PAHs, polycyclic aromatic hydrocarbons; PhIP, 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine; SEER, Surveillance Epidemiology and End Results.

Introduction

Non-Hodgkin lymphoma (NHL) is the fifth most common cancer in men and women in the United States (1); there are several established risk factors, largely related to immunodeficiency, but they do not account for the majority of cases. This malignancy has generated increased interest as the incidence rates have nearly doubled in the last three decades and known risk factors are not sufficiently common to explain such an increase (2).

Dietary associations with NHL have not been extensively investigated. An association between dietary fat or protein and NHL is biologically plausible as both may cause deleterious effects on the immune system. Recently, several studies have focused on fat and protein intake in relation to NHL. Both case–control and cohort studies have found excess risks in the highest quantile of total fat and saturated fat intake (3–5). In addition, a recent large cohort study reported a 1.7-fold increased risk for NHL in the highest quintile of animal protein intake (3).

Red meat has been associated with cancers at a variety of sites, including the colorectum, stomach, pancreas, breast, prostate and kidney (6). Meat is a source of both saturated fat and animal protein and, depending on the cooking method and the doneness level, several classes of potential carcinogens. Meat cooked well-done using high-temperature cooking techniques is a source of heterocyclic amines (HCAs) and polycyclic aromatic hydrocarbons (PAHs) (7–9). HCAs and PAHs have been shown to induce tumors, including lymphomas, in animals at a variety of sites (10–12). The second hypothesis, in contrast to the HCA and PAH hypothesis, is based upon findings from previous studies that have found a risk associated with meat cooked rare and that well-done meat intake is inversely associated with NHL risk (5,13). Rare meat may be a source of viruses or other contaminants that would be destroyed only by prolonged cooking or cooking at a higher temperature.

We conducted a case–control study to estimate the effect of meat intake, cooking method, doneness level, and estimated HCA and PAH intake on the risk of developing NHL.

Materials and methods

Study participants

Individuals were recruited from four areas of the USA: three counties in the Detroit metropolitan area in Michigan (Macomb, Oakland and Wayne Counties); two counties in the Seattle metropolitan area of Washington State (King and Snohomish); the state of Iowa; and Los Angeles County in California. These four geographic areas are served by NCI-sponsored Surveillance

Epidemiology and End Results (SEER) registries, which were used to identify all the residents with a first primary diagnosis of NHL between July 1998 and June 2000. To be eligible for this study, all participants had to be aged 20–74 years and not be infected with the human immunodeficiency virus. All the 1321 newly diagnosed NHL cases were histologically confirmed and classified, according to the latest World Health Organization scheme (ICD-O-2 based on SEER codes); for this analysis, all cases were collapsed into four pathologic groups: follicular, diffuse, T-cell and the fourth category encompassed all other classifications.

Controls aged ≤65 years were selected using one-step list-assisted random digit dialing (14). Controls aged 65–74 years were identified from the Center for Medicare and Medicaid Services files of residents eligible for Medicare. In total, 1057 controls with no previous diagnosis of NHL were recruited and matched to cases by age (5 years), center, race and gender.

Data collection

The study was approved by the human subjects review boards at all participating institutions and all participants provided written informed consent.

The participants were randomly assigned to one of the two study arms, except the African-American participants who were all assigned to the 'non-diet' arm of the study; the purpose of this design was to ensure a sufficient number of individuals from this racial group with the same questionnaire data. The study reported here included only individuals in the 'diet' arm of the study, which involved a computer-assisted personal interview, including questions on education, occupation, smoking behavior, history of cancer and other diseases and focused on cell phone use, sunlight and allergies; participants were also sent a self-administered dietary questionnaire. The dietary questionnaire was a 117-item food frequency questionnaire (FFQ) regarding the frequency of consumption and portion size information for their usual diet over the past 12 months. This questionnaire was based on the Block 1995 Revision of the Health Habits and History Questionnaire (15,16). Information on the frequency of consumption and portion size of meat was obtained for various meat groups. Information on cooking method and doneness level for hamburger, steak, pork chops, bacon and sausage were obtained using a meat picture card showing varying degrees of doneness. For these meats, we calculated the intake of three HCAs: 2-amino-3,4,8-trimethylimidazo[4,5-f]quinoxaline (DiMeIQx), 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MeIQx) and 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP), as well as the PAH benzo[a]-pyrene (B[a]P), using the data from the FFQ linked to a HCA and PAH database (http://charred.cancer.gov/). In addition, this database was used to determine mutagenic potential, which is a measure of total mutagenic potential from meat and, therefore, incorporates all meat-related mutagens.

Among participants assigned to the 'diet' arm of the study, 482 of the 552 cases and 417 of the 462 controls returned the dietary questionnaire. Two other cases and two other controls inadvertently received and returned the dietary questionnaire and are included in the analysis, giving a total of 484 cases and 419 controls. Individuals were excluded from the analysis if they reported consuming <4 foods per day in the case of males, <3 foods per day in the case of females, >30 foods in the case of both males and females or if they left >20% of foods blank, these exclusions applied to 46 individuals. The extreme outliers for caloric intake were also excluded from the analysis and were considered to be those in the top and bottom 1% of reported total caloric intake ($n = 16$). Some individuals fell into more than one exclusion category, leaving 458 NHL cases and 383 controls for the analysis.

Statistical analysis

Odds ratios (ORs) and 95% confidence intervals (CI) were computed using unconditional logistic regression, using the first quartile as the referent group. We chose cut points for all of the dietary data from the distribution among the controls and trend tests were calculated using the median intake values of each of these quartiles. Variables with a mean intake of <5 g/day (red meat cooked rare, red meat broiled) were split into binary variables, comparing consumers with non-consumers. The statistical models were adjusted for gender, age (<35, 35–44, 45–54, 55–65 and >65 years), study center, non-occupational physical activity (none, 30–270, 271–675, 676–1080 and >1080 metabolic equivalent tasks per week) and alcohol intake (g/week); additionally, total caloric intake (kJ/day) was included in the model, as a continuous variable, to help to reduce the measurement error associated with over-reporting or under-reporting of dietary components. The models for fat were adjusted for caloric intake using the nutrient density method. The individual HCAs and B[a]P were modeled independently of each other and were also adjusted for animal protein (grams/day). The following potential confounders were added to the model and were proved not to affect the risk estimates and therefore were not included in the final models: ethnicity (White, Asian and other), educational attainment (<12 years, 12–15 years and ≥16 years), body mass index (<20, 20–24, 25–30 and >30 kg/m^2), family history of NHL, smoking status (current, former and never smoker), history of farming job (never, current and former) and servings of fruits and vegetables.

Table I. Characteristics of cases and controls

Characteristics	Cases $N = 458$ *n* (%)	Controls $N = 383$ *n* (%)	*P*-value*
Gender			0.24
Male	249 (54.4)	191 (49.9)	
Female	209 (45.6)	192 (50.1)	
Age			0.0001
<35	25 (5.5)	11 (2.9)	
35–44	59 (12.9)	32 (8.4)	
45–54	97 (21.2)	59 (15.4)	
55–64	128 (27.9)	96 (25.1)	
65+	149 (32.5)	185 (48.3)	
Study center			0.68
Detroit	52 (11.4)	47 (12.3)	
Los Angeles	101 (22.1)	78 (20.4)	
Iowa state	173 (37.8)	134 (35.0)	
Washington state	132 (28.8)	124 (32.4)	
Race			0.61
White	433 (94.5)	370 (96.6)	
Asian	16 (3.5)	7 (1.8)	
African-American	0 (0)	0 (0)	
Other	9 (2.0)	6 (1.6)	
NHL pathologic type			
Follicular	115 (25.1)	—	
Diffuse	165 (36.0)	—	
T-cell	23 (5.0)	—	
Other	155 (33.8)	—	
Physical activity (metabolic equivalent tasks/week)			0.14
None	83 (18.1)	54 (14.1)	
30–270	108 (23.6)	82 (21.4)	
271–675	92 (20.1)	81 (21.1)	
676–1080	68 (14.8)	80 (20.9)	
>1080	83 (18.1)	74 (19.3)	
Missing data	24 (5.2)	12 (3.1)	
Alcohol intake (g/week)	38.4 (87.6[a])	47.6 (98.3[a])	0.003[b]
Mean caloric intake (kJ/day)	1906.2 (691.4[a])	1782.1 (628.6[a])	0.009[b]

*P-value derived from the chi-squared test unless otherwise indicated.
[a]Standard deviation.
[b]P-value derived from the chi-squared test the Wilcoxon signed rank sum test.

Results

Cases on whom we had the dietary data tended to be younger than controls (Table I). More cases were males and tended to be less physically active than controls and consumed more calories but drank less alcohol.

Within the control group the mean intake of red meat was higher than the intake of white meat (89 compared with 56 g/day) (Table II). The most common cooking method for the five selected meat items was barbecuing and pan-frying, with a mean intake of 13 and 10 g/day, respectively, and then broiling, with a mean of 4 g/day (Table II). Other cooking methods, such as microwaving and baking, were less common, with a mean intake of 1 and 2 g/day, respectively (data not shown). Preference of doneness level of meat ranged from rare through medium to well-done, although the mean intake of red meat cooked rare was only 4 g/day (Table II).

The HCAs consumed in the highest quantity within the control group were PhIP and then MeIQx (means: 141 and 43 ng/day, respectively) (Table III). DiMeIQx and MeIQx were most highly correlated with well-done meat intake

Table II. Intake of meat variables (g/day) among controls ($n = 383$)

Variables	Mean	SD	Median	10th percentile	90th percentile
All meat	145.7	84.7	128.4	62.1	260.6
Red meat	89.4	64.8	72.1	24.1	183.8
Red meat using a known cooking method	35.5	27.7	29.1	5.1	75.0
Barbecued red meat	13.2	17.9	6.9	0	38.7
Pan-fried red meat	10.2	14.6	5.3	0	28.5
Broiled red meat	3.7	7.5	0	0	10.9
Rare red meat	3.8	9.3	0	0	12.0
Rare/medium red meat	15.4	19.5	8.6	0	43.6
Medium red meat	11.5	16.8	3.7	0	34.0
Well-done red meat	17.2	20.2	9.6	0	48.0
White meat	56.4	42.6	47.3	15.0	106.4
Chicken	22.4	22.5	14.0	0	45.5
Fish	6.0	11.5	2.8	0	12.9
Tuna	8.1	10.6	5.1	0	21.7
Processed meat[a]	18.6	18.9	12.2	0.5	43.0
Protein	76.2	28.1	70.0	45.8	113.8
Protein from animal sources	52.2	24.7	48.0	25.8	85.1
Protein from plant sources	24.9	11.2	23.4	12.5	39.3
Fat	70.5	32.2	63.6	34.8	114.5
Saturated fat	24.2	11.6	22.1	12.1	40.6
Unsaturated fat	46.3	21.4	42.1	23.3	75.1
Oleic acid	27.3	13.1	24.7	13.3	45.5
Linoleic acid	12.9	6.8	11.3	5.8	22.0

[a]Includes bacon, sausage, ham, hotdogs, liver and luncheon meats.

Table III. Estimated intake of HCA and B[a]P among controls ($n = 383$)

Variables	Mean	SD	Median	10th percentile	90th percentile
DiMeIQx (ng/day)	3.8	7.1	2.0	0.1	8.0
MeIQx (ng/day)	42.9	61.2	23.6	4.0	98.5
PhIP (ng/day)	140.7	208.4	73.8	3.6	340.6
B[a]P (ng/day)	37.1	54.4	16.8	0.8	91.8
Mutagenicity (revertant colonies/day)	8173	19907	4921	931	15667

($r = 0.32$ and 0.52, respectively). PhIP and B[a]P were most highly correlated with barbecued red meat ($r = 0.42$ and 0.72, respectively). Within the HCAs, DiMeIQx and MeIQx were highly correlated ($r = 0.89$) and their correlation with PhIP was 0.70 and 0.69, respectively.

There was a significantly elevated risk for NHL in the highest quartile of total fat intake (Table IV); however, the trend was not significant (P trend = 0.12). In contrast, protein intake was inversely associated with the risk for NHL [OR and 95% CI: 0.38 (0.20–0.75), P trend = 0.01], an effect that was driven by animal sources of protein [OR and 95% CI: 0.39 (0.22–0.70), P trend = 0.004] and not plant sources [OR and 95% CI: 1.00 (0.57–1.75), P trend = 0.72] (Table IV). The main contributors to the animal protein variable in this dataset were milk (17%), hamburgers (8%), chicken (7%), steak (6%), eggs (5%) and cheese (4%), with other meats and dairy products contributing smaller amounts.

There were no associations between total meat consumption or the consumption of red or white meat and NHL risk (Table IV). The consumption of broiled meat was associated with a modest, but not statistically significant, elevation in risk compared with those who did not consume broiled meat [OR and 95% CI: 1.32 (0.99–1.77), P trend = 0.09] (Table IV). There was also a suggestive positive association across increasing quartiles of well-done red meat consumption and NHL risk (P trend = 0.08) (Table IV). In contrast, there was a modest, inverse association for NHL across the quartiles of barbecued red meat and fish consumption (P trend = 0.07 and 0.08, respectively) (Table IV).

Neither MeIQx, PhIP or B[a]P were associated with NHL; however, the highest quartile of DiMeIQx was unexpectedly inversely associated with risk of NHL [OR and 95% CI: 0.63 (0.41–0.97), P trend = 0.03] (Table V). The combined mutagenicity of these meat-related mutagens was assessed using a mutagenic potential score; this score did not reveal a significant association with NHL. Overall the associations for NHL-were generally similar within the major subtypes with adequate numbers for assessment, follicular, diffuse large B-cell and T-cell.

Discussion

In this population-based case–control study, we found no association between red meat, white meat or processed meat and risk for NHL. Protein from animal sources and DiMeIQx were inversely associated with risk for NHL; furthermore, there was a suggestion of an inverse association for barbecued red meat and fish intake. In contrast, well-done red meat and broiled red meat were associated with a modest non-significant increased risk for NHL.

The strengths of this study included the population-based design and exceptional detail on meat intake and meat preparation methods. The dietary questionnaire used in this study had many questions dedicated to meat-cooking practices to estimate the intake of meat-related mutagens. This is also the first study to specifically address HCAs and PAHs with respect to risk for NHL. In addition, this study had sufficient statistical power (>80%) to detect an odds ratio of 1.7, which was the risk found for animal protein and red meat in the previous studies (3,5).

The limitations of this study included the loss of information due to non-response, as well as the likely errors in recalling and reporting usual dietary intake. The NHL cases collected their dietary data after their diagnosis and, therefore, their diet may have changed since the onset of the disease and may no longer represent the diet prior to the development of NHL. In addition, the assessment of usual diet using FFQs is associated with an inherent degree of measurement error, which may attenuate results.

Previous studies have focused on fat and protein intake as risk factors for NHL. The rationale behind the fat and protein hypotheses is based upon their ability to affect the immune system. In animal models dietary fat suppresses the immune system (17) and large amounts of protein can result in immune unresponsiveness (18) as a result of chronic hyperstimulation (19). Some, but not all, case–control and cohort studies have observed an increased risk for NHL associated with fat intake (3–5). The findings for protein are more inconsistent, a risk of 1.4 was found for total protein and a risk of 1.7 for animal protein in a case–control study of 601 women (3), but no associations were found in two cohort studies (5,13) or in the most recent case–control study of 1642 NHL cases (4). Our study found a significantly elevated risk for NHL in the highest quartile of fat intake. In contrast, we observed a

Table IV. OR and 95% CI for NHL risk associated with the intake of meat variables*

Variables	Q2	Q3	Q4	*P* trend[a]
All meat	1.04 (0.69–1.57)	0.98 (0.64–1.50)	0.71 (0.42–1.20)	0.14
Red meat	1.00 (0.65–1.52)	1.24 (0.80–1.91)	1.10 (0.67–1.81)	0.87
Red meat with known cooking method	1.10 (0.71–1.69)	0.92 (0.58–1.45)	0.75 (0.45–1.25)	0.15
Barbecued red meat	0.92 (0.61–1.38)	0.79 (0.53–1.20)	0.67 (0.44–1.03)	0.07
Pan-fried red meat	0.77 (0.50–1.18)	1.08 (0.71–1.65)	1.18 (0.75–1.84)	0.11
Broiled red meat	1.32 (0.99–1.77)[b]	–	–	0.09[b]
Rare red meat	0.87 (0.64–1.20)[b]	–	–	0.33[b]
Rare/medium red meat	0.68 (0.44–1.06)	1.13 (0.77–1.68)	0.69 (0.45–1.06)	0.14
Medium red meat	0.59 (0.30–1.15)	1.14 (0.79–1.66)	0.92 (0.62–1.35)	0.57
Well-done red meat	0.75 (0.48–1.16)	1.13 (0.74–1.73)	1.17 (0.73–1.86)	0.08
White meat	0.68 (0.46–1.02)	0.57 (0.37–0.86)	0.76 (0.50–1.16)	0.26
Chicken	1.03 (0.68–1.55)	0.85 (0.56–1.30)	0.79 (0.51–1.23)	0.28
Fish	1.02 (0.66–1.57)	0.68 (0.45–1.03)	0.73 (0.49–1.10)	0.08
Tuna	1.39 (0.91–2.11)	1.24 (0.82–1.88)	1.18 (0.76–1.82)	0.74
Processed meat[c]	1.36 (0.89–2.06)	1.32 (0.86–2.03)	1.18 (0.74–1.89)	0.94
Protein	0.50 (0.32–0.77)	0.61 (0.39–0.97)	0.38 (0.20–0.75)	0.01
Protein from animal sources	0.57 (0.37–0.87)	0.65 (0.42–1.01)	0.39 (0.22–0.70)	0.004
Protein from plant sources	1.13 (0.73–1.73)	0.76 (0.47–1.22)	1.00 (0.57–1.75)	0.72
Fat[d]	1.47 (0.97–2.23)	1.36 (0.89–2.06)	1.60 (1.05–2.45)	0.12
Saturated fat[d]	1.60 (1.03–2.51)	1.30 (0.80–2.12)	1.37 (0.82–2.29)	0.66
Unsaturated fat[d]	1.47 (0.94–2.28)	1.55 (0.97–2.46)	1.43 (0.86–2.39)	0.18
Oleic acid[d]	1.25 (0.72–2.17)	1.71 (0.85–3.43)	1.49 (0.64–3.43)	0.07
Linoleic acid[d]	1.13 (0.72–1.80)	0.90 (0.53–1.53)	1.04 (0.57–1.87)	0.61

*Models were adjusted for gender, study site (Los Angeles, Detroit, Seattle and Iowa state), age (<35, 35–44, 45–54, 55–65 and >65 years), physical activity (none, 30–270, 271–675, 676–1080 and >1080 metabolic equivalent tasks per week), total caloric intake (kcal/day) and alcohol consumption (<1, ≥1–15, >15–30 and >30 g/day)
[a]*P* trend calculated using the median of each quartile.
[b]Comparing those who consume this meat with those who do not.
[c]Includes bacon, sausage, ham, hotdog, liver and luncheon meats.
[d]Fat models were adjusted for energy intake using the nutrient density method.

Table V. OR and 95% CI for NHL risk associated with the intake of HCAs and B[a]P*

Variable	Q2	Q3	Q4	*P* trend[a]
DiMeIQx	0.90 (0.60–1.34)	0.75 (0.49–1.12)	0.63 (0.41–0.97)	0.03
MeIQx	1.03 (0.68–1.55)	1.21 (0.80–1.85)	1.01 (0.64–1.61)	0.94
PhIP	0.90 (0.60–1.35)	0.77 (0.50–1.17)	0.73 (0.46–1.16)	0.19
B[a]P	0.76 (0.50–1.14)	0.81 (0.53–1.23)	0.73 (0.46–1.14)	0.34
Mutagenic potential	1.18 (0.78–1.79)	1.12 (0.73–1.73)	0.82 (0.50–1.35)	0.20

*Models were adjusted for gender, study site (Los Angeles, Detroit, Seattle and Iowa state), age (<35, 35–44, 45–54, 55–65 and >65 years), physical activity (none, 30–270, 271–675, 676–1080 and >1080 metabolic equivalent tasks per week), total caloric intake (kcal/day), alcohol consumption (<1, ≥1–15, >15–30 and >30 g/day) and animal protein (g/day).
[a]*P* trend calculated using the median of each quartile.

significant inverse association with protein intake, specifically animal protein intake, and risk for NHL.

Meat comprises both fat and protein and is also a source of mutagenic compounds, such as *N*-nitroso compounds formed during the preservation process, as well as HCAs and PAHs formed during cooking. A previous case–control study (20) and a cohort study (5) found an increased risk for NHL in the highest tertile of red meat consumption, the cohort study identified that the main component contributing to this risk was hamburgers. In contrast, a recent case–control study did not find a risk associated with the consumption of red meat *per se*, but did find an elevated risk of NHL in the highest tertile of processed meat consumption (4). Our study did not find an association with red meat, processed meat or hamburgers.

The degree to which meat is cooked has previously been associated with NHL; women in Iowa who cooked their meat well-done had a significantly lower risk of NHL compared with those who preferred their meat cooked medium-rare or rare (5). This was not a finding replicated in our study; however, meat-cooking information in the Iowa study was obtained in a follow-up questionnaire, administered 6 years after the baseline questionnaire and their analysis was based on only 67 NHL cases. The issue of dietary change in response to disease status is inherent to case–control studies, and therefore this issue also applies to our study. In addition, a weak inverse association between well-done meat and the risk of NHL was observed in the Nurses' Health Study cohort (13). An association between meats consumed rare and NHL risk may be the result of under-cooked meat being a source of contaminants such as viruses; however, this study does not support such association.

The hypothesis relating HCAs and PAHs to NHL would predict increased risks associated with well-done meats cooked using high-temperature cooking methods. Our study found a modest, but not statistically significant, increase in risk across quartiles of well-done meat consumption, although the increments were small and could have arisen by chance. With regard to the cooking method, we observed a 32% increased risk associated with the consumption of broiled red meat, although this did not quite reach statistical significance; this finding is in agreement with a previous cohort study (13). The mechanism to explain any such association with broiled meat, but not other meats cooked at high temperatures, is unclear.

There was no risk of NHL associated with the consumption of barbecued red meat, in which the highest amounts of HCAs and PAHs are formed. The observations regarding the intake

levels of HCAs in this study are in agreement with previous studies in that PhIP and MeIQx are the most common and that DiMeIQx and MeIQx are highly correlated. Feeding experiments in rodents have shown that HCAs can induce immunotoxicity (21); furthermore, feeding PhIP and MeIQx to rodents is associated with an increased risk of lymphoma (10–12). However, this study did not find a positive association between any of the HCAs measured and the risk of NHL. In contrast to the expectations, DiMeIQx was associated with an inverse association with NHL, although it is not clear why such an association should exist.

B[a]P was the PAH assessed in this study and we would expect this to be present in the highest quantities in barbecued/grilled red meat, with which it was highly correlated ($r = 0.72$). These meat-related compounds are surrogates for the doneness of the meat and a previous study found an inverse association for well-done meat intake (5); however, there was no association for meat cooked rare, although the consumption of meats cooked in this way was very low in this study, or B[a]P and risk of NHL.

In conclusion, data from this case–control study suggests that meat and meat cooked using high-temperature cooking methods are not associated with an elevated risk of developing NHL. Furthermore, this is the first study to investigate meat-related mutagens with regard to NHL and the findings showed that a high intake of HCAs or B[a]P was not associated with an elevated risk of this disease. Additional studies, especially prospective studies, may help to confirm or refute the present observations.

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